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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 04/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,979	DE JONG ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32,34-47,59,61-64 and 144-147* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,26-32,34,35,41-43,47,59,61-64,144-147* is/are rejected.

7)☒ Claim(s) *16-25,36-40 and 44-46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 18 March 2005 in response to the Final Office Action mailed 28 December 2004. Claims 1-32, 34-47, 59, 61-64 and 141-147 were considered in the 28 December Office Action. Claims 141-143 were canceled and claim 1 was amended in the 18 March Paper. Claims 1-32, 34-47, 59, 61-64 and 144-147 are presently pending and under consideration.

Finality of the previous Office Action is hereby **withdrawn** in view of the new grounds for rejection set forth herein below.

Response to Amendment

Rejection of claims 141-143 is rendered moot by the cancellation thereof.

Rejection of claims 1-32 and 144-146 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 11 and 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in reciting that the agent "increases contact between the nucleic acid molecule and the cell" and "enhances permeability of the cell", and claim 11 is indefinite in reciting, "applying an agent to the cell that enhances permeability". "Increases" and "enhances" are relative terms which do not have a definite meaning unless a standard for comparison is provided. For example, an agent might enhance permeability of a cell relative to one set of conditions but have no effect on permeability of a cell relative to a different set of conditions.

Claim 26 is indefinite in reciting steps (a) and (b) that are different from the steps (a) and (b) set forth in claim 1, from which claim 26 depends.

Claim 28 is indefinite in reciting, "the energy is ultrasound". Claim 25, from which claim 28 depends, limits the energy to electrical energy. Therefore, there is no antecedent for energy that is ultrasound in claim 25.

Claims 27 and 29 are indefinite insofar as they depend from claims 26 and 28, respectively.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34, 35, 41-43 and 47 rejected under 35 U.S.C. 102(b) as being anticipated by Unger *et al.* (1997) *Invest. Radiol.* 32:723-727 (made of record in the IDS filed 7 September 2001) as evidenced by the Mediatech, Inc. Formulations Table for Dulbecco's Modification of Eagle's Medium available at www.cellgrow.com (hereinafter, Mediatech DMEM formulation).

Unger *et al.* teaches a method for introducing a nucleic acid molecule into a cell comprising applying ultrasound energy to the cell in the absence of the nucleic acid molecule

(see especially the 30 min pretreatment point in Figure 4) and then contacting the cell with the nucleic acid molecule whereby the nucleic acid molecule is delivered into the cell. In the paragraph bridging pages 723-724, Unger teaches that the ultrasound is applied to the cells by immersing the head of the ultrasound transducer into the cell culture medium. The limitation "delivery agent" is defined on page 13 of the specification as, "compositions, conditions or physical treatments to which cells and/or nucleic acids may be exposed in the process of transferring nucleic acids to cells in order to facilitate nucleic acid delivery into cells". As the culture medium can reasonably be viewed as a composition that facilitates nucleic acid delivery into cells because it provides a medium through which the nucleic acid is contacted with the cell, the method of Unger *et al.* also comprises contacting the cell in the absence of the nucleic acid molecule with a delivery agent. Therefore, the method of Unger *et al.* comprises each of the elements of the instant claims 34 and 41.

Furthermore, as the culture medium used in the method of Unger *et al.* (*i.e.*, DMEM) comprises cationic compounds such as arginine and lysine (see the Mediatech DMEM formulation), the method of Unger *et al.* also anticipates the method of claim 35. In addition, in the method of Unger *et al.*, the cells were exposed to ultrasound energy at between 0.1 and 1 W/cm^2 (*i.e.*, 0.5 W/cm^2) for 30 seconds in a continuous pulse according to claims 42 and 43 (see especially the caption to Figure 4 and the paragraph bridging pages 723-724). Finally, claim 47 limits the cell into which the nucleic acid is introduced to a nuclear donor cell. As the specification provides no limiting definition of a nuclear donor cell, the cell of the claim is construed, according to the broadest reasonable interpretation, as encompassing any cell that

could donate a nucleus (*i.e.*, any nucleated cell). As the cell used in the method of Unger *et al.* comprises a nucleus, the method of Unger *et al.* also anticipates the instant claim 47.

The method of Unger *et al.* is the same as the method of the instant claims 34, 35, 41-43 and 47; therefore, the claims are properly rejected under 35 USC §102(b) as anticipated by the art.

Claims 1-4, 6, 7, 9, 10, 12-14 and 30-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Marschall *et al.* (1999) *Gene Ther.* 6:1634-1637 as evidenced by Lipofectamine™ Reagent product description, available from Invitrogen™ life technologies or Transfectam™ Reagent product description, available from Promega.

Marschall *et al.* teaches a method for introducing large nucleic acids such as 2.3 Mb yeast artificial chromosomes into eukaryotic cells by lipofection using Lipofectamine™ or Transfectam™ reagent (see especially the first full paragraph on page 1636, Table 1 and the caption thereto). On page 2, the Lipofectamine™ Reagent product description teaches that the procedure for transfection using the Lipofectamine™ reagent comprises contacting a nucleic acid molecule to be delivered with a delivery agent (*i.e.*, Lipofectamine™; step 2), contacting the cell with a delivery agent (*i.e.*, serum-free growth medium; step 3) and contacting the cell with the nucleic acid molecule. In part III A., the Transfectam™ Reagent product description teaches that the procedure for transfection using Transfectam™ reagent comprises contacting cells with a delivery agent (*i.e.*, serum-free medium) and in part III C., the product description teaches that the procedure comprises contacting a nucleic acid molecule with a delivery agent (*i.e.*, Transfectam™) and then contacting the cell with the nucleic acid molecule. Thus, the method of

Marschall *et al.* as evidenced by the Lipofectamine™ Reagent or Transfectam™ Reagent product description comprises all of the elements of the instant claim 1.

With regard to claim 2, because no benchmark is provided to establish the metes and bounds of increasing contact between the nucleic acid and the cell or enhancing permeability of the cell (*Id.*), the limitations are read broadly. Clearly the Lipofectamine™ and Transfectam™ reagents of Marschall *et al.* increase contact between the nucleic acid and the cell and, because the aqueous medium is required for establishing the proper interface between the nucleic acid delivery agent and the cell membrane, the serum-free medium of Marschall *et al.* is construed as enhancing permeability of the cell.

Furthermore, in the method of Marschall *et al.*, the nucleic acid is greater than about 1 megabase according to claims 3 and 4; the nucleic acid is an artificial chromosome according to claims 6 and 7; the molecule is contacted with the delivery agent *in vitro* according to claim 9; the nucleic acid is contacted with the cell *in vitro* according to claim 10; the Lipofectamine™ reagent comprises DOSPA and DOPE according to claims 12-14 (Lipofectamine™ Reagent product description page 1) and the Transfectam™ reagent comprises DOGS according to claims 12 and 13 (Transfectam™ Reagent product description page 1); the cells are human HT1080 fibrosarcoma cells (see especially the caption to Figure 2), which cells anticipate the animal cell of claim 30 and the nuclear donor cell (see claim construction discussed above), immortalized cell, transformed cell and tumor cell of claims 31 and 32.

The method of Marschall *et al.* as evidenced by the Lipofectamine™ Reagent and Transfectam™ Reagent product descriptions, is the same as the method of the instant claims 1-4,

6, 7, 9, 10, 12-14 and 30-32; therefore, the claims are properly rejected under 35 USC §102(b) as anticipated by the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 12-14, 30-32, 59, 61-64 and 144-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hadlaczky *et al.* (2/2000) US Patent No. 6,025,155 (previously made of record) in view of Marschall *et al.* (*supra*) as evidenced by Lipofectamine™ Reagent product description (*supra*) or Transfectam™ Reagent product description (*supra*).

Hadlaczky *et al.* describes artificial chromosomes and teaches that the artificial chromosomes can be introduced into cells using lipid mediated transfer (paragraph bridging columns 5 and 6). The method of Hadlaczky *et al.* comprises: delivery of a nucleic acid molecule that is greater than about 5 megabases according to claims 2-5 (see throughout, especially the second full paragraph in column 9); wherein the nucleic acid molecule is an artificial chromosome expression system (*ACes*) according to claims 6-8 (Hadlaczky *et al.* refers to the chromosomes as SATAC's, which the instant specification teaches is interchangeable with the term *ACes*; see the first full paragraph on page 11 of the specification); wherein the chromosome is delivered into any of a variety of cells including plant cells, animal cells, tumor cells and embryonic stem cells according to claims 30-32 (see especially the section entitled "2. Hosts" beginning in column 21); and wherein the chromosome can be in the range of about 90 to about 120 megabases or about 15 to about 50 megabases according to claims 144-146 (see especially the second full paragraph in column 9).

Hadlaczky *et al.* does not teach a particular method by which the artificial chromosomes can be introduced into cells using a lipid mediated transfer system.

As described above, Marschall *et al.* teaches a method for introducing large nucleic acids into eukaryotic cells by lipofection using Lipofectamine™ or Transfectam™ reagent, which method comprises sequentially contacting a nucleic acid molecule to be delivered with a delivery

agent, contacting the cell with a delivery agent and contacting the cell with the nucleic acid molecule. Marschall *et al.* does not teach an artificial chromosome that is greater than about 5 megabases according to claim 5 or within the size ranges set forth in claims 144-146 and does not teach a nucleic acid molecule that is an *ACes* according to claim 8.

The combined teachings of Hadlaczky *et al.* and Marschall *et al.* as evidenced by the Lipofectamine™ Reagent or Transfectam™ reagent include all of the elements set forth in the instant claims and establish that the materials and process steps necessary to practice the instant claimed invention were available to the skilled artisan at the time the invention was made. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Hadlaczky *et al.* to include the particular method steps set forth in the method of Marschall *et al.* as evidenced by the Lipofectamine™ Reagent or Transfectam™ Reagent product descriptions according to the limitations of the instant claims. One would be motivated to combine these teachings in view of the nature of the problem to be solved in the method of Hadlaczky *et al.* (*i.e.*, to deliver large nucleic acid molecules into eukaryotic cells) and the demonstrated effectiveness of the method of Marschall *et al.* in delivering large nucleic acids into cells.

Furthermore, the method of claims 59, 61-64 and 147 would also be obvious to one of ordinary skill in the art in view of the teachings set forth in Hadlaczky *et al.* and Marschall *et al.* as evidenced by the Lipofectamine™ Reagent or Transfectam™ reagent. Claim 59 is directed to a method for delivering a large nucleic acid molecule into a cell comprising contacting the nucleic acid molecule with a composition that comprises DOSPA and DOPE, wherein the nucleic acid is at least 5 megabases. As described above, the lipofectamine reagent used in the

method of Marschall *et al.* comprises DOSPA and DOPE. Furthermore, as is also described above, the nucleic acid molecule of Hadlaczky *et al.* is an artificial chromosome according to claim 62, the cell of the Hadlaczky *et al.* is any of a variety of cells including plant cells, animal cells, tumor cells and embryonic stem cells according to claims 62 and 63; Marschall *et al.* teaches that the nucleic acid is contacted with the cell *in vitro* according to claim 64; and the chromosome of Hadlaczky *et al.* is about 10 megabases to about 450 megabases according to claim 147. Thus, the invention of claims 59, 61-64 and 147, as a whole, would also have been obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 16-25, 36-40 and 44-46 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER